REMARKS

Claims 1, 9, 13, 15, and 19-24 are pending in the application. Claim 1 has been cancelled by this amendment. New claims 31-33 have been added to the application. Therefore, claims 9, 13, 15, 19-24, and 31-33 are at issue.

The courteous interview granted to applicant's undersigned attorney and inventor Gulati by Examiners Padmanabhan and Carter on June 23, 2009 is hereby acknowledged with appreciation. At the interview, the claims, Office Action, cited references, and proposed claim amendments were discussed in detail.

By this amendment, claim 1 has been cancelled and claim 9 has been rewritten as an independent claim. In particular, claim 9 has been amended to incorporate features from now-cancelled claim 1. Claim 9 also has been amended to recite that the method is directed to the amelioration of Alzheimer's disease in a human suffering from the disease. Support for the amendments to claim 9 can be found in original claim 1 and by the specification at page 6, lines 8-11. New claims 31-33 are supported by the specification at page 26, line 28 through page 27, line 5; page 28, lines 16-27; and page 29, lines 23-32.

Claim 9, the sole independent claim, recites ameliorating Alzheimer's disease in a human suffering from the disease by administering a therapeutically effective amount of bosentan. In particular, the present invention is *not* directed to a cure for Alzheimer's disease. Independent claim 9 particularly recites "ameliorating" Alzheimer's disease to clarify the effect of bosentan on this disease.

A person suffering from Alzheimer's disease will not be freed from the disease by the present method. The present method *does* treat adverse effects or symptoms resulting from Alzheimer's disease by addressing the issue of a reduced blood flow to the brain caused by Alzheimer's disease. The present method overcomes the vasoconstriction associated with Alzheimer's disease and improves a blood flow in the brain. This difference between cure and treatment must be kept in mind when considering the patentability of the presently claimed method because statements in the Office Action appear to equate cure and amelioration.

Claims 1 and 9 stand rejected under 35 U.S.C. §103 as being obvious over Hughes et al. U.S. Patent Publication 2003/0040534 ('534) in view of a Wu publication (Wu). Claims 13, 15, and 19-24 stand rejected under 35 U.S.C. §103 as being obvious over the '534 publication in view of Wu, and further in view of Woolf U.S. Patent No. 5,466,696 ('696). For the reasons set forth below, it is submitted that these rejections are in error and should be withdrawn. The rejection of claim 1 is moot in view of the cancellation of claim 1.

THE '534 PUBLICATION

The '534 publication discloses one specific endothelin antagonist, wherein the (+) dextrorotatory atropisomer has a much higher potency than the (-) levorotary atropisomer or the racemate ('534 publication, abstract). The '534 publication also discloses that the compounds are antagonists of ET-1, ET-2, and/or ET-3, and are useful in the treatment of conditions associated with increased ET levels and *all* endothelin-dependent disorders ('534 publication, paragraph [0011]). The '534 publication then recites a myriad of conditions that may be treated using the disclosed endothelin antagonist of the '534 publication ('534 publication, paragraphs [0012] through [0018]).

The '534 publication specifically teaches that the disclosed compounds are antagonists of ET-1, ET-2, and/or ET-3, which more properly classifies the compounds as ET_B antagonists. Further, binding to ET_A receptors as discussed in the '534 publication fails to instruct as to whether the compound is an ET antagonist or an ET agonist. The information in the '534 publication therefore is totally insufficient to classify the disclosed antagonist because only binding to ET_A is demonstrated. In particular, the Wu publication cited against the claims states that selective ET_A receptors binds as follows: ET-1>>ET-2~ET-3, whereas non-selective ET_B receptors bind as follows: ET-1~ET-2~ET-3 (page 1653). Further, Wu states that endothelin antagonists are classified as follows: ET_A selective means selectivity for ET_A over ET_B is >100 fold; ET_B selective means ET_B over ET_A is >10 fold; and the rest are considered to be ET_A/ET_B antagonists (page 1654). As discussed below, the '534 publication merely shows that the disclosed compounds bind to the ET_A receptor with no data as to binding to the ET_B receptor.

The '534 publication states that the disclosed compound is an endothelin antagonist. The reference further discloses that the compounds "are antagonists of ET-1, ET-2, and/or ET-3", which essentially is the definition of an ET_B receptor antagonist (see Wu publication discussion below). Although the '534 publication demonstrates binding of the compound to ET_A receptors, this does not equate to the compound being a selective ET_A inhibitor. The reference fails to provide any tests with respect to ET_B bonding. Accordingly, no conclusion can be made as to which type of endothelin antagonist the compound of the '534 publication belongs. Further, mere binding to ET_A receptors fails to define the compounds as an antagonist or an agonist.

More particularly, the '534 publication provides data showing *in vitro* binding of the enantiomers of the compound, i.e., the disclosed compounds bind to endothelin A (ET_A) receptors. These receptors are expressed by CHO-K1 cell used in the test ('534 publication, column 5, paragraph [0034]). The '534 publication shows that the sole compound disclosed in the reference binds to ET_A receptors, but the reference discloses nothing more. The '534 publication also fails to tie this binding to *any*, let alone *all*, of the diseases and conditions set forth at paragraphs [0012]-[0018] of the reference. The diseases vary greatly in identity and etiology, i.e., from cancer, to skin disorders, to arthritis, to lupus and fibrosis, to sickle cell diseases, and beyond. The '534 publication therefore is no more than a bald conclusion that the disclosed compound can treat each disease state cited in the reference.

THE WU PUBLICATION

The Wu publication is a review article that identifies and classifies various endothelin antagonists. As stated above, the endothelin antagonists were classified using an arbitrary criteria based on selectivity of compounds for ET_A receptors over ET_B receptors (Wu publication, page 1654, left column). Wu also discloses the following in the Introduction, at page 1653:

> "There are two distinct types of endothelin receptors cloned: the ET-1 selective ET_A receptors (binding ET-1 >> ET-2 ~ ET-3) primarily found on vascular smooth muscle and responsible for vasoconstriction; and the non-selective ET_B

receptors (binding ET-1 ~ ET-2 ~ ET-3) primarily found in vascular endothelium and responsible for vasodilation."

The Wu publication also discloses that "[D]ue to the vasodilative properties of ET_B receptors" only a limited number ET_B selective antagonists were discovered (page 1658, right hand column). The Wu publication also states that ET_B selective compounds "are not beneficial" (page 1665, left hand column). This statement is incorrect, as discussed below.

The Wu publication also contains Table 1 at page 1665, listing ET_A and ET_A/ET_B antagonists that were under clinical development. Although all the compounds are ET_A or ET_A/ET_B antagonists, the compounds are being tested for a *variety* of *different* diseases and conditions of *different* etiologies, e.g., prostate cancer, congestive heart failure, myocardial infarction, hypertension, renal failure, and four other diseases. No single compound was being tested for more than three diseases. The Wu publication, in Table 1, therefore shows that *no single* endothelin antagonist (ET_A or ET_A/ET_B) is contemplated as being useful for all disease states, as suggested in the '534 publication. In addition, the table teaches that an ET_A antagonist and an ET_A/ET_B antagonist are being tested for the treatment of *different* diseases, except for congestive heart failure and hypertension. Accordingly, the Wu publication table shows that an ET_A antagonist is useful in the treatment of some diseases, whereas an ET_A/ET_B antagonist is useful in the treatment of others. Therefore, the efficacy of an ET_A antagonist *cannot* be equated to the efficacy of an ET_A/ET_B antagonist in the treatment of the same disease, and efficacy of a specific endothelin antagonist against a specific disease is unpredictable.

PROPER BASIS FOR AN OBVIOUSNESS REJECTION UNDER 35 U.S.C. §103

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness under 35 USC §103 is determined by: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of non-obviousness.

Furthermore, to establish a prima facie case of obviousness, the examiner must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR*

International Co. v. Teleflex Inc. et al., 127 S.Ct. 1727 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason* to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to *identify* a *reason that would have prompted a person of ordinary skill in the relevant field to combine the elements* in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (emphasis added, *KSR*, *supra*). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. In *re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

To reach a proper determination under 35 U.S.C. §103(a), the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to the person. Knowledge of applicants' disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search, and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicants' disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the *facts* gleaned from the prior art. MPEP §2142.

The Supreme Court identified a number of rationales that may be used to support a conclusion of obviousness, consistent with the framework set forth in its decision in *Graham v. John Deere Co.* See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739-40

(2007). These and other representative rationales are described at MPEP §2143 (8th Ed., Rev. 6, Sept. 2007). Regardless of the supporting rationale the Patent Office must clearly articulate facts and reasons why the claimed invention "as a whole" would have been obvious to a person at ordinary skill in the art at least as of the claimed invention's effective filing date. See *KSR Int'l*, 127 S.Ct at 1741 (citing with approval In *re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")); see also MPEP §2143 ("The key to supporting any rejection under 35 USC §103 is the clear articulation of reason(s) why the claimed invention would have been obvious.").

The rational relied upon by the examiner apparently is as follows:

"B. Simple Substitution of One Known Element for Another To Obtain Predictable Results

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

(1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;

(2) a finding that the substituted components and their functions were known in the art;

(3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious *is that the substitution of one known element for another would have yielded predictable results* to

> one of ordinary skill in the art at the time of the invention. *If any of these findings cannot be made, then this rationale cannot be used* to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." (Federal Register, Vol. 72, No. 195, page 57530, Oct. 10, 2007, emphasis added)

THE PENDING CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER THE COMBINATION OF CITED REFERENCES

The basis of the present rejection is that the '534 publication teaches an endothelin antagonist that can bind to ET_A receptors. The '534 publication further states that the disclosed compound is an antagonist of ET-1, ET-2, and/or ET-3[1]. In addition, the '534 publication purports that the disclosed compound can treat "all endothelin dependent disorders," followed by a listing of a myriad of disorders of different etiologies, including the treatment of Alzheimer's dementia.

In addition, Wu discloses a large number of endothelin antagonists, classified as ET_A, balanced ET_A/ET_B, and ET_B receptor antagonists, and discloses disease states treated by endothelin antagonists, e.g., congestive heart failure, pulmonary hypertension, and renal failure. In this extensive review article of endothelin antagonists, Wu fails to disclose the treatment of *any* dementias. It should be noted that bosentan, as disclosed in Wu is in clinical trials *only* for congestive heart failure.

The examiner then reasons that it would have been obvious to substitute bosentan disclosed in Wu for the compound disclosed in the '534 publication in an amelioration of Alzheimer's disease. Applicants traverse the examiner's reasoning because the substitution propounded by the examiner is not suggested by the combination of references and the results of the substitution would not have been predictable.

In particular, the '534 publication generalized the use of one specific endothelin inhibitor in the treatment of *any* disorder that is purportedly endothelin related. However, it is widely known that there are two types of endothelin receptors, ET_A and ET_B. ET_A receptors are potent vasoconstrictors; and ET_B receptors are well known as potent

[1] As discussed above, the totality of this information fails to inform a person skilled in the art as to whether the disclosed compounds is an ET_A antagonist or an ET_A agonist, or whether the disclosed compound an ET_A, ET_B, or ET_A/ET_B antagonist.

vasodilators. Hence, ET_A and ET_B receptors act opposite to one another. Supporting publications for these statements, and those that follow, were provided to the examiner in previously-filed Amendment "B". The examiner is also directed to page 12 of previously-filed Amendment "B" detailing differences that arise due to inhibition of ET_A receptors vs. inhibition of ET_B receptors. Thus, it is well known that inhibition of ET_A receptor or ET_B receptors, or both, can produce different effects.

The '534 publication discloses the use of CHO-K1 cell expressing ET_A receptors to show bonding of the disclosed compound (paragraphs [0033]-[0037]). The reference therefore demonstrates binding of the disclosed compound to ET_A receptors, but not to ET_B receptors *because no testing was performed* for ET_B binding. Thus, it is unknown whether the disclosed compound has a greater binding affinity for ET_A or ET_B receptors, and as a result it is unknown whether the compound disclosed in the '534 publication is an ET_A, ET_B, or ET_A/ET_B receptor antagonist using the criteria of the Wu publication. Importantly, the '534 publication fails to state that the disclosed compound is an ET_A receptor antagonist, and provides insufficient facts to conclude that it is an ET_A receptor antagonist.

In addition, the '534 publication states that the disclosed compounds "are antagonists of ET-1, ET-2 *and/or* ET-3" (paragraph 11, emphasis added). It is also noted that non-selective ET_B receptors bind approximately equally to ET_1, ET_2, and ET_3, as disclosed in Wu (Introduction, page 1653). Therefore, the compound disclosed in the '534 publication may be an ET_B receptor antagonist based on the above statement in the '534 publication at paragraph 11.

Further, and importantly, the '534 publication has merely demonstrated *binding* of the disclosed compound to ET_A receptors. The reference provides no teaching as to whether the compound is an agonist or an antagonist of ET_A. Some compounds bind to an ET_A receptor and inhibit the receptor (antagonism); other compounds bind to an ET_A receptor and activate the receptor (agonism). Accordingly, the compound of the '534 publication may inhibit or may *activate* ET_A. The reference states that the compound is an endothelin antagonist, but provides no guidance, and it cannot be concluded that the compound inhibits ET_A. The reference further provides absolutely no guidance with respect to bonding to ET_B receptors, and then whether the compound should be classified as an ET_A, ET_A/ET_B, or ET_B

receptor antagonist. The presently claimed compound is known as an ET_A/ET_B inhibitor and is useful in the amelioration of Alzheimer's disease symptoms and adverse effects.

The present claims recite bosentan, i.e., a compound that antagonizes both ET_A and ET_B, and is useful in the amelioration of Alzheimer's disease symptoms and adverse effects. The '534 publication fails to show that the compound is an ET_A antagonist, or to teach that the disclosed compound is a mixed ET_A/ET_B antagonist. In fact, the compound may be an ET_B antagonist. The reference therefore provides a person skilled in the art no incentive or apparent reason to select an ET_A/ET_B receptor antagonist, and particularly bosentan, as a substitute for the endothelin receptor antagonist disclosed in the reference.

Furthermore, the '534 publication purports a treatment of the diseases disclosed in paragraphs [0012]-[0018]. This disclosure *lists more than 125 different classes and specific diseases and conditions* that are purportedly treated by the compound disclosed in the '534 publication. The '534 publication fails to provide *any* evidence that *each* of these classes of and specific disease are endothelin related. This disclosure in the '534 publication therefore is no more than pure speculation and hoped for efficacy, and is unsupported by any facts that all the disclosed diseases and conditions can be treated by the disclosed compound.

To demonstrate that all conditions disclosed by the '534 publication are not treatable by an endothelin antagonist, the examiner is directed to applicants' copending application number 10/301,449, published as U.S. Patent Publication 2003/0100507 ('507 publication). The '534 publication, at paragraph [0013], states that the purported endothelin antagonist treats pain. The '507 publication however clearly shows that endothelin antagonists, e.g., BQ123 and BMS182874 (both selective ET_A antagonists, see Wu), do *not* alleviate pain, as asserted in the '534 publication at paragraph [0013]. See '507 publication, paragraphs [0082]-[0084] and Figs. 2-6, for example, wherein the tail flick method shows no pain alleviation by administration of an endothelin antagonist. These results show that the '534 publication disclosure is a hoped for efficacy for the myriad of diseases named in the publication. Also see the attached Gulati Declaration (Exhibit A), filed in copending application September 11, 2008, and particularly paragraphs 13-18.

The Wu reference does not overcome the deficiencies of the '534 publication with respect to using an endothelin antagonist recited in the claims to treat Alzheimer's disease in a human. The Wu reference is relied upon for a teaching of various endothelin antagonists, and that bosentan is in clinical trials (*only* for congestive heart failure, which is unrelated to Alzheimer's disease). First, it must be noted that bosentan is *not* in clinical trials relating to Alzheimer's disease. The fact that bosentan is in clinical trials is irrelevant with respect to the claims at issue. Further, as discussed above, Table 1 of the Wu publication lists nine other ET_A and ET_A/ET_B antagonists undergoing clinical trials for different diseases (none of which is related to dementia) and the ten different compounds are in clinical trails for different diseases, i.e., different antagonists treat different diseases.

Wu is a review article that teaches, identifies, and classifies various endothelin antagonists. In particular, Wu discloses 109 compounds, none of which are disclosed as treating *any* dementia. Notably, Wu does *not* teach or suggest the use of any of 109 endothelin antagonists in the treatment of Alzheimer's Disease or any other dementia. The '534 publication discloses the treatment of dementias no more than in passing. Therefore, a person skilled in the art, even with the '534 publication and the Wu reference before him, still would have had *no* apparent reason to make the leaps in reasoning discussed above with respect to the '534 publication and thereby arrive at the presently claimed invention.

In particular, where is the incentive or apparent reason for a person skilled in the art to select bosentan from the 109 compounds of Wu, and use the claimed compound in connection with *one* of the 125 different classes and specific disease disclosed in the '534 publication, with any reasonable expectation of successfully ameliorating Alzheimer's disease? This is especially true in view of Table 1 of the Wu publication, which shows the unpredictability in this art.

At page 7 of the Office Action, the examiner states that applicant has attacked the references individually, rather than in combination. Applicant respectfully disagrees. Applicant notes that a proper analysis for obviousness requires that "[T]he scope and content of the prior art are...determined; differences between the prior art and the claims at issue are...ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham v. John Deere Co.* 148 U.S.P.Q. 459 (1966). This analysis *must* include a discussion of the

prior art on which the examiner is relying. Just as the examiner has addressed the references individually in setting out the rejection, applicant offers in rebuttal a discussion of what the individual references disclose. This rebuttal discussion cannot be construed as an attack on the references individually. It is simply a discussion of what the individual references disclose, so as to ascertain whether the combined teachings support the examiner's assertion of obviousness.

The examiner's rejection is based on a reasoning that is a *fait accompli* that using *any* compound of Wu (total of 109) would be useful in treating any disease disclosed in the '534 publication (total of greater than 125). However, Table 1 of Wu shows the opposite. Individual endothelin antagonists are used to treat different diseases, with very little overlap. Individual selective ET_A antagonists are useful for treating different diseases, individual ET_A/ET_B antagonists also are useful for treating different diseases, and ET_A antagonists treat different diseases than balanced ET_A/ET_B antagonists.

The examiner refers to an "obvious to try rationale" at page 10 of the Office Action. The examiner is reminded that to support a conclusion of obviousness using this rationale, there must be a recognized need in the art, a finite number of *predictable* potential solutions, and a reasonable expectation of success. The Wu publication teaches 109 potential solutions, and shows that *different* solutions, i.e., different endothelin antagonists, are used to solve different problems, i.e., treat different diseases. See, Table 1 of Wu, discussed above. If the art is predictable, why are different endothelin antagonists in clinical trials for different diseases? Following the logic of the examiner, every drug in Wu should treat every disclosed condition in the '534 publication. This logic cannot be supported based on Table 1 of Wu, and applicant's copending application, showing that an endothelin antagonist does *not* treat pain, even though the '534 publication states, without proof, that an endothelin antagonist treats pain. Contrary to the examiner's unsubstantiated statement, unpredictability and expectation of success to support in obvious to try rationale are not provided by a combination of the '534 publication and Wu.

Further, although the '534 publication implies that Alzheimer's dementia is associated with increased ET levels and therefore is treatable using the compound disclosed in the '534 publication, prior studies showed that levels of ET-1 in the cerebrospinal fluid of

patients of Alzheimer's disease is *lower* compared to controls (Yoshizawa et al., 1992 *Neuropeptides*, *vol 22*: page 85-88). Later reports showed increased expression of ET-1 in the astrocytes of the brain of Alzheimer's disease patients (Jiang et al., *Neuroreport vol 4*: page 935-937; Zhang et al., 1994 *J. Neurol. Sci. vol 122*, page 90-96). It also was found that oligodendrocytes and endothelial cells of blood vessels of control and Alzheimer's disease cases do not show ET-1 immunoreactivity (Zhang et al., 1994 *J. Neurol. Sci. vol122* page 90-96).

All these studies show the unpredictability in the art of ET's and the results of inhibition of ET, in a particular organ, to treat a specific disease. This unpredictability coupled with the large number of compounds disclosed in Wu, and the vast number of diseases disclosed in the '534 publication, renders the present claims non-obvious over a combination of the '534 publication and Wu regardless of whether the examiner is relying upon a substitution rational or an obvious to try rationale.

In addition, the Court in *KSR* held that a factfinder should be aware of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct., 1727, 1742 (U.S. 2007). The examiner may be utilizing the teachings of the specification in an attempt to combine the references to allegedly arrive at the claimed invention. Applicants respectfully note that MPEP §§2142 and 2143 require that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 4899 (Fed. Cir. 1991). The mere fact that the prior art may be modified in the manner suggested by the examiner does *not* make the modification obvious unless the prior art suggests the desirability of the modification. *In re Gordan*, 733, F.2d at 902, 221 USPQ at 1127. *In re Fritch*, 23 USPQ 2nd 1780, 1783-1784 (Fed. Cir. 1992). It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Gorman*, 933 Fed. 2nd 982, 987, 18 USPQ 2nd 1885, 1888 (Fed. Cir. 1991). *In re Fritch*, 23 USPQ 2nd 1780 at 1784 (Fed. Cir. 1992).

To arrive at the present invention, person skilled in art would have had to select one of 109 compounds of Wu to treat one of 125 diseases listed in the '534 publication.

This selection of a compound and disease is not provided by the combination of references, but rather by applicant's own disclosure. The examiner has provided no reasoning why a person skilled in the art would have an apparent reason an incentive to select Alzheimer's disease from the 125 diseases stated of the '534 publication and bosentan from the 109 compounds of Wu, unless brought to this selection by applicant's disclosure.

Therefore, in view of (a) the vague teachings of the '534 publication with respect to how the disclosed compound should be classified (i.e., agonist or antagonist, or ET_A, ET_B, or ET_A/ET_B antagonist), (b) the vast number of diseases and conditions, of different etiologies, disclosed in the '534 publication, and (c) the large number of different compounds disclosed in Wu, what would lead a person skilled in the art to select a particular endothelin antagonist (i.e., bosentan) with any reasonable expectation of ameliorating Alzheimer's disease symptoms?

In addition, the examiner's statement at page 9 of the Office Action that positive responses are not known for antagonizing both ET_A or ET_B receptors, i.e., ET_B antagonists are not beneficial, is traversed. The action of ET-1 and participation of its receptors varies in different organ systems. It has been shown, for example, that alveolar fluid clearance in the lung is reduced 65% by ET-1. It further was found that ET-1 induced inhibition of alveolar fluid clearance was completely prevented by the ET_B receptor antagonist BQ788, whereas the ET_A receptor antagonist, BQ123, had no effect (Berger et al., 2009, *Anesth Analg, vol 108*: pages 225-231). Therefore, it is clear that ET_B receptors do have positive role to play in various functions of the body.

It cannot be assumed, and the examiner has not supported, that the biological effects of ET_A receptor stimulation is similar to ET_B receptor stimulation, and that ET_A receptor stimulation is similar to ET_A/ET_B receptor stimulation. The role of each receptor is unique as provided by evidence that darunsentan, a specific ET_A receptor antagonist, has been found to be highly effective in the treatment of resistant hypertension, while *no* other ET antagonist has been found to have similar effect (Enseleit et al., 2008; *Expert Opin Investig Drugs vol 17*: page 1255-1263). Hence, there is unpredictability in the art, i.e., persons *a priori* have no reasonable expectation that substituting one ET antagonist for another will treat a specific disease.

Applicant also does not agree that ET_B receptors are not beneficial, and therefore they have no significance. The binding sites for ET-1 in rat brains with ischemia and in human brains with Alzheimer's disease were mapped by quantitative autoradiography. The ET-1 binding sites are decreased in the cerebral cortex of Alzheimer's disease and these binding sites could be blocked by BQ788 (ET_B antagonist) and not by BQ123 (ET_A antagonist) indicating the presence of ET_B receptors and not ET_A receptors (Kohzuki et al., 1995 *J. Cardiovasc Pharmacol, vol 26*, page S329-S331).

In summary, for all of the reasons set forth above, it is submitted that present claim 9 is patentable over a combination of the '534 publication and the Wu reference. Accordingly, this rejection of claim 9 under 35 U.S.C. §103 should be withdrawn. It is further submitted that new claims 31 and 32 are patentable over the '534 publication in view of the Wu publication for the reasons set forth above.

With respect to the rejection of claims 13, 15 and 19-24 over a combination of the '534 publication, Wu, and the '696 patent, the examiner relies upon the '696 patent for a teaching that cholinesterase inhibitors are known to treat dementias. Claims 13, 15 and 19-24 recite preferred embodiments of the present invention. However, applicant does not rely upon the administration of a cholinesterase inhibitor to treat AD as the sole point of patentability.

Applicant relies upon all the features recited in claims 13, 15, and 19-24 *and* the claim from which they depend, i.e., claim 9, for patentability. The '696 patent fails to overcome the deficiencies of the '534 publication and Wu with respect to treating a human suffering from Alzheimer's Disease with an endothelin antagonist. Therefore, claims 13, 15 and 19-24 are patentable over a combination of the '534 publication, Wu, and the '696 patent, for the same reasons claim 9 is patentable over a combination of the '534 publication and Wu. Accordingly, the rejection of claims 13, 15, and 19-24 under 35 U.S.C. §103 should be withdrawn. It is further submitted that new claim 33 is patentable over a combination of the '534 patent, the Wu publication, and the '696 patent for the reasons set forth above.

It is submitted that the claims are now in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Dated: November 4, 2009

Respectfully submitted,

By _____

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